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A CONTRIBUTION TO THE PATHOGENESIS OF THE CHANGES IN THE COLLAGEN-GROUND SUBSTANCE EQUILIBRIUM IN MORPHOEA (SCLERODERMA).*

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WHEN one examines a section of the skin stained with eosin the collagen bundles are seen to be separated from one another by spaces. McMaster and Parsons (1950) state that it is generally agreed that this appearance is almost certainly misleading and that shrinkage occurs during the process of dehydration, producing artificial spaces which probably do not exist during life. They showed that if interstitial spaces, filled with free fluid, exist normally they must be much smaller than the spaces seen in microscopic sections. Consequently, one concludes that the collagenous matrix of the dermis really consists of true collagen surrounded by a slight amount of ground substance (Figs. 1, 2 and 3).

In the following account the term "collagen-ground substance mass" is employed because it is not possible to distinguish collagen from ground substance in the normal adult skin corium (excluding basement membranes) with the stains used in this work.

FIG. 1 to 3.—Normal skin. Formol fixation. $\times 430$.

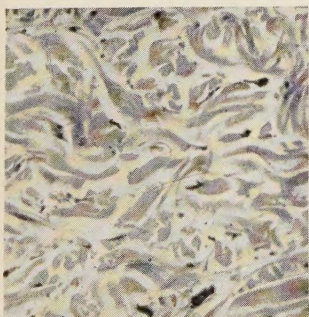


FIG. 1.—Normal collagen-ground substance masses H. & E.

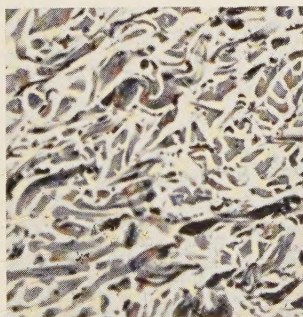


FIG. 2.—Normal elastic tissue. Sheridan's ET.

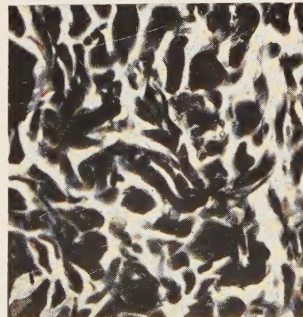


FIG. 3.—Normal collagen-ground substance masses. Van Gieson

* Adapted from a paper read at the 33rd Annual Meeting of the British Association of Dermatology held in London on 25 June 1953.

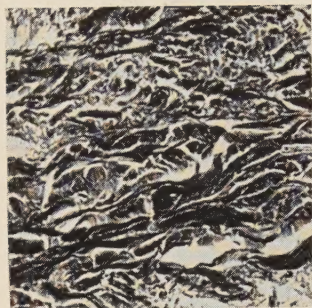


FIG. 4.—Normal skin. Buffer control. No significant effect. Van Gieson. $\times 430$.

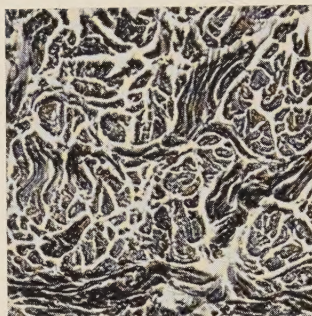


FIG. 5.—Normal skin. Very slight effect of trypsin on collagen-ground substance masses. Van Gieson. $\times 430$.

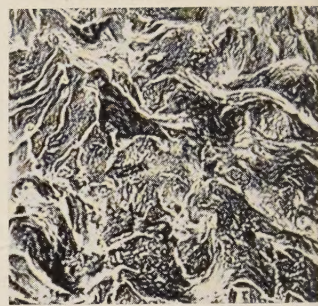


FIG. 6.—Morphoea. Buffer control. This shows the most advanced degree of clearing seen in the three buffer controls of morphoea. Van Gieson. $\times 430$.

HISTOLOGY OF MORPHOEA.

The changes occur in stages as follows :

Stage 1.—The collagen-ground substance masses increase in width, pushing apart the elastic tissue fibres which are otherwise unaltered. The tissue artefact spaces are reduced in width. One might say that at this stage the essential architecture of the reticular part of the corium is preserved, though exaggerated (Figs. 7, 8 and 9).

Stage 2.—The collagen-ground substance masses tend to appear as irregular bands sometimes arranged in parallel rows. Individual masses often seem to have fused producing larger masses which stain more or less evenly eosinophile with haematoxylin-eosin; with van Gieson, however, definite tissue artefact spaces are still visible with no faintly staining material in the spaces themselves. The elastic tissue seems to be of normal amount with more than normal separation of individual fibres (Figs. 11, 12 and 13).

Stage 3.—Between newly formed collagen-ground substance masses there are lighter similarly coloured areas in which can be seen the fine fibrillary appearance characteristic of young collagen. There is varying diminution of elastic tissue at this stage (Figs. 15, 16 and 17).

Stage 4.—In this, the most advanced stage, areas of connective tissue are formed which resemble hyaline degeneration and stain mostly uniformly with eosin. There is some evidence that these areas contain darker stained collagen-ground substance masses surrounded by lighter coloured areas when stained with van Gieson. Elastic tissue is much reduced (Figs. 21, 22 and 23).

When resolution takes place, the excess material is absorbed leaving histologically normal collagen-ground substance and elastic tissue. It is suggested not that the skin is now completely normal, but that histologically at least

these two components may return to an essentially normal appearance when the process finally ends.

THEORY PROPOSED TO ACCOUNT FOR THE ABOVE HISTOLOGICAL CHANGES.

It is suggested that the changes in the reticular part of the corium in morphoea are produced as the result of an increase in the amount of ground substance,

FIG. 7 to 10.—Morphoea. Stage 1. $\times 430$.

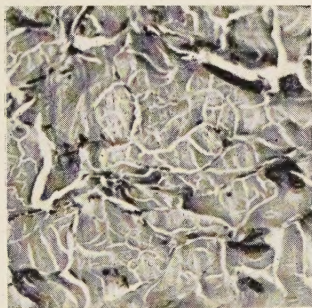


FIG. 7.—Note increased width of the collagen-ground substance masses. H & E.

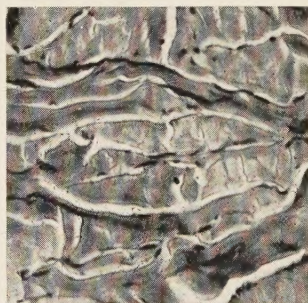


FIG. 8.—Elastic tissue normal in amount but further apart than normal. Sheridan's ET.



FIG. 9.—Appearance with van Gieson.

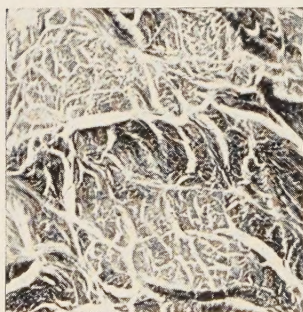


FIG. 10.—After trypsin treatment. Note marked fine fibrillation and persistence of the bulk of the collagen-ground substance masses. Van Gieson.

and that the ground substance is not fully polymerized but is otherwise normal. The mechanism involved in its deposition is unknown.

In Stage 1 the amount of the ground substance deposited is not in excess of the ability of the tissue to utilize it and to convert it into collagen. The chief change at this stage is therefore the formation of new collagen with a slight excess of ground substance left behind; apparently the ground substance does not produce new elastic tissue.

In Stage 2, the ground substance is deposited more quickly than the tissues can use it and the result is that although new collagen formation has occurred, there is a fair amount of ground substance still present which fills in the "gaps" between the collagen-ground substance masses and elastic tissue.

In these first two states the deposition of excess ground substance is in the site where it is normally found, i.e., around already existing collagen-ground

FIG. 11 to 14.—Morphoea. Stage 2. $\times 430$.

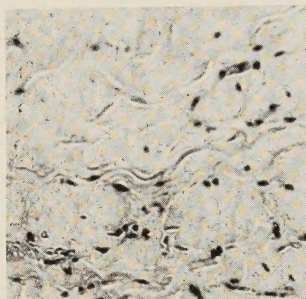


FIG. 11.—More or less evenly staining area with few tissue spaces. H & E.

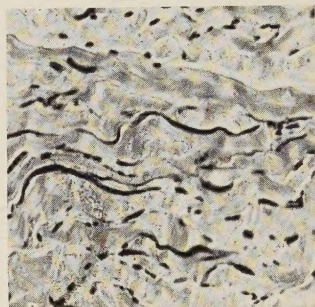


FIG. 12.—Normal amount of elastic tissue somewhat further apart than normal. Sheridan's ET.

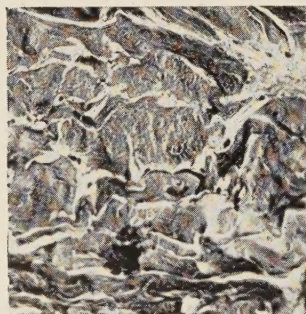


FIG. 13.—Tissue artefact spaces clearly visible with van Gieson.

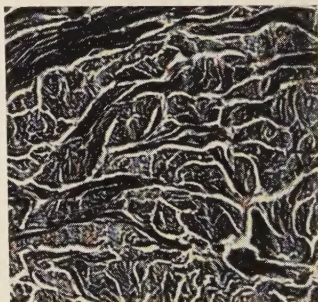


FIG. 14.—After trypsin treatment. Note very numerous tissue artefact spaces, marked fine fibrillation and persistence of the collagen-ground substance masses. Van Gieson.

substance masses and elastic tissue. In the next two stages, on the other hand, it is laid down in "pools" around, between, or independently of the pre-existing fibrillary structures, the greatest amount being deposited in Stage 4. It is suggested that in these two stages there is new collagen formation, the process more approaching the normal in Stage 3.

It is important to note that the whole process takes place without the intervention of greatly increased numbers of fibroblasts such as occurs in the for-

FIG. 15 to 18.—Morphoea. Stage 3. $\times 430$.

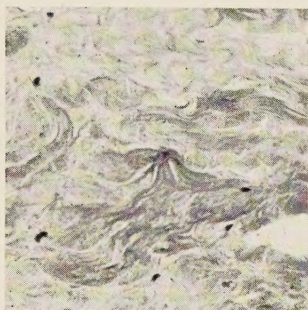


FIG. 15.—Note lighter coloured areas between the darker collagen-ground substance masses. H & E.

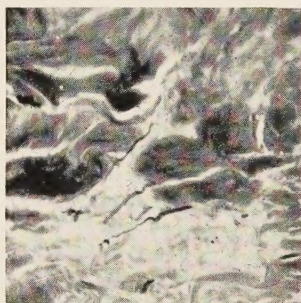


FIG. 16.—Almost complete absence of elastic tissue. Sheridan's ET.

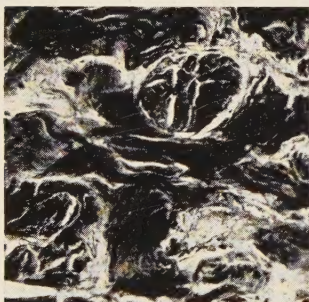


FIG. 17.—Some evidence of fine fibrillation in the lighter areas. Van Gieson.



FIG. 18.—After trypsin treatment. Note normal collagen-ground substance masses but of increased size surrounded by lighter staining areas which are partly finely fibrillar. Van Gieson.

FIG. 19 and 20.—Morphoea. Stage 3. $\times 1000$.

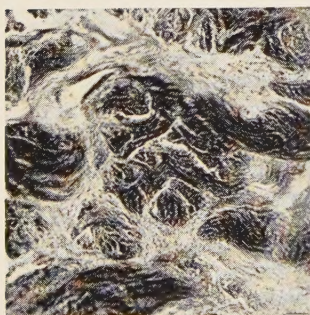


FIG. 19.—Part of area similar to Fig. 18. The lighter staining areas show a fine fibrillar appearance. Van Gieson.

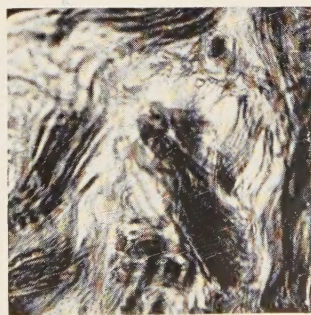


FIG. 20.—As for Fig. 19 but stained by Mallory.

FIG. 21 to 24.—Morphoea. Stage 4. $\times 430$.

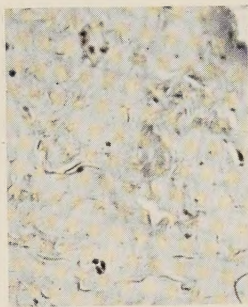


FIG. 21.—Note hyalin-like area with little distinct structure. H & E.

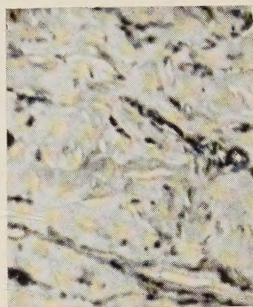


FIG. 22.—Reduced amount of elastic tissue. Sheridan's ET.



FIG. 23.—Van Gieson.



FIG. 24.—After trypsin treatment on an area probably similar to that of Fig. 23. Considerable clearing is evident. Van Gieson.



FIG. 25.—The same as Fig. 24. Very extensive fine fibrillation with the Mallory stain. $\times 1000$.

mation of scar tissue, though in the last two stages fibroblasts may wander into these areas from neighbouring places.

It seems that the ground substance is formed into collagen by the action of such fibroblasts as are present and that also, under appropriate physico-chemical conditions, this change will take place without fibroblasts. In morpoea both processes may be at work, for the process of fibrous tissue formation seems to be different from the formation of collagen in scar tissue.

It is noted that in the last two stages elastic tissue is not formed at least in the normal amount, though perhaps it is formed at a still later stage when the collagen has reached a more adult arrangement.

INVESTIGATIONS.

Four specimens of normal skin and material from eight cases of morpoea and three of resolving morpoea were used. Seven of the scleroderma specimens and all the normal skin specimens were submitted to the action of trypsin and subsequently processed as given in the appendix.

Three of the scleroderma specimens and all those of normal skin were submitted to the action of the undiluted buffer solution alone; further details are given in the appendix at the end of the paper.

RESULTS OF TREATMENT WITH TRYPSIN.

1. *Buffer Controls.*

(a) *Normal Skin.*

There are no significant changes in the structural appearance of the collagen-ground substance masses with van Gieson or in the elastic tissue (Fig. 4).

(b) *Morpoea.*

There may be some clearing compared with the untreated controls when examined with van Gieson, but the appearance was not that described below for morpoea after trypsin treatment. The elastic tissue is unaffected (Fig. 6).

2. *Trypsin Treated Material.*

(a) *Normal skin.*

The collagen-ground substance masses are essentially unchanged with van Giëson. The elastic tissue may be partly or completely absent (Fig. 5).

(b) *Morpoea.*

Stage 1.—A marked fine fibrillation of the collagen-ground substance masses becomes visible with van Gieson. Although some ground substance has been removed, by far the greater part of the collagen-ground substance masses remains behind and this residue appears to be nearly all collagen. It is to be noted

that there are no marked gaps in the section, which would be expected if the trypsin had removed a considerable amount of necrotic collagen. There is a reduction in the intensity of the staining by van Gieson in the trypsin treated section as compared with the control (Figs. 9 and 10).

Stage 2.—In this phase, showing the almost fused eosinophilic mass with haematoxylin-eosin but with tissue artefact spaces clearly visible with van Gieson, there become obvious very numerous tissue artefact spaces, and marked fine fibrillation and persistence of the collagen-ground substance masses (Figs. 13 and 14). No specimens were available to show the effects on the irregularly layered appearance sometimes seen in this stage.

Stage 3.—The large collagen-ground substance masses show marked fibrillation. The fine fibrils in the lighter areas are better seen, but there is some substance left between them which may be collagen at an earlier stage of development. The collagen of the large collagen-ground substance masses and the fine fibrils are probably newly formed (cf. Fig. 17 with Figs. 18 to 20).

Stage 4.—The effect produced is very similar to that in Stage 3 after the same treatment except that there has been more ground substance removed in Stage 4 (cf. Fig. 23 with Figs. 24 and 25).

In the scleroderma tissue submitted to the action of the two specimens of commercial trypsin used, it was found that the elastic tissue was digested to an extent varying from none up to complete digestion. This signifies that some unknown factor or factors were at work to produce a variable activity of the elastase which contaminates commercial trypsin. However, the effect of trypsin on the ground substance was quite independent of the degree of digestion of elastic tissue. Variable elastase action was observed also on the specimens of normal skin.

DISCUSSION.

From the effects of trypsin on morphoea as stated above, three facts are evident: (1) A "covering" substance is removed which can be shown to have the staining reactions of normal adult ground substance (2) most of the ground substance extractable is more easily extractable than in normal skin; and (3) there is increase in the bulk of the collagen bundles already present in Stages 1 and 2 with new formation of collagen in Stages 3 and 4. In the following discussion an attempt will be made to account for these facts.

The ground substance of normal skin can be tentatively visualized as a jelly-like material in which are embedded the fibrillary structures—collagen, elastic tissue and reticulin—and the skin appendages. It completely fills all the space between these structures so that there are no free tissue spaces *in vivo*, and the tissue slits seen in histological preparations are artefacts. Under the electron-microscope it appears to be of amorphous nature; chemically it consists of protein and carbohydrate, there being considerably greater amounts of an

unknown carbohydrate material in the basement membranes at the dermo-epidermal junction and around the skin appendages. In staining properties it is non-metachromatic (i.e., does not resist alcohol dehydration after suitable staining with toluidine blue), stains red with eosin, blue with Mallory and red with van Gieson—that is to say, the collagen coloured by these stains includes some ground substance though the amount of collagen far exceeds the amount of ground substance. The McManus reaction stains the basement membranes a deep red colour and the collagen-ground substance masses a much fainter uniform red colour.

It is suggested that the substance removed by trypsin in morphoea is normal ground substance, for it stains in the same way except that in the lighter areas in Stages 3 and 4 it is mixed with fine fibrils of young collagen and a mass which is probably collagen at a still earlier stage of formation.

It is possible under certain conditions to remove with trypsin the protein element of the ground substance from the normal skin. Electronmicroscopic studies (Tunbridge *et al.*, 1952) have demonstrated that such treatment “cleans” the fibrils without otherwise altering their electronmicroscopic appearance. Gersh and Catchpole (1949) found that on freeze-dried material the fibrils freed in this way from ground substance did not stain like normal fibrils with the Hotchkiss reaction. In the histological preparations of normal skin described in this paper, treatment with trypsin did not materially alter the staining reaction of the collagen; this means that little ground substance could be extracted from normal adult skin under the conditions described.

Gersh and Catchpole (1949) found that in the rat the ground substance is extracted with increasing difficulty in older animals until eventually none can be extracted. They attribute this to a progressive increase in the degree of polymerization of the ground substance as the animal gets older. In morphoea the fact that the ground substance is susceptible to the action of trypsin may mean either that it is at an earlier stage of formation or that it is depolymerized as the result of a degenerative process. It is most unlikely that ground substance depolymerized through disease would be capable of producing new collagen, and the view that the ground substance in morphoea is at an earlier stage of formation or polymerization than normal is more acceptable.

Fibroblasts in tissue culture in electronmicroscopic preparations have been shown to be capable of producing thin collagen fibrils from a medium completely free from protein, but the addition of protein to the medium increases the amount and maturity of the collagen so formed (Porter, 1951). On the other hand Wyckoff (1952) showed the gradual formation of a nearly normal collagen fibril as seen in the electronmicroscope from structureless material in an acetic acid solution of tendon precipitated with pH 4.6 citrate buffer without there being any possibility of action of fibroblasts. Further, Highberger *et al.*, (1951)

have shown that by varying the proportion of mucoprotein to the filtrate of an acetic acid solution of collagen, long spacing, or normal collagen fibrils or both are formed, and can be seen in the electronmicroscope; at a certain concentration of mucoprotein, fibrils of normal width can be produced. Watson and Pearce (1949) have found that as the amount of fibrous tissue increases in patients with localized myxoedema of the legs, the amount of hyaluronic and chondroitin sulphuric acids extractable is considerably reduced, i.e., as collagen formation increases some constituents of the ground substance decrease. There is further experimental evidence to show that collagen is not formed immediately as such but is derived from non-fibrous soluble protein (procollagen) (Harkness, 1952).

It is not unreasonable to assume, therefore, that the increased amount of ground substance in morphoea can form the stratum for the fibroblasts to form increased collagen. On the other hand, ground substance when deposited under appropriate physico-chemical conditions might spontaneously form collagen in a way comparable with the mucoprotein-acetic acid mixture of Highberger *et al.* Both processes may play a part in morphoea.

It is realized that trypsin may remove necrotic collagen and therefore the material removed in these experiments might be necrotic collagen; but it is considered in view of the above data that it is most unlikely that necrosis of collagen is the fundamental or primary process in morphoea.

APPENDIX.

Biopsy material from 7 cases of scleroderma was treated either at once or after being kept in normal saline in the refrigerator for varying periods up to six weeks. The specimens were then cut in half, one part being fixed in absolute acetone in the refrigerator for 10 to 21 hours, dehydrated with absolute acetone at room temperature for 13 to 24 hours, cleared in two changes of benzene for a total of 2 to 3 hours, and embedded in wax at 56° C. for 2 to 6½ hours. The other halves of the specimens were placed in 1% commercial trypsin in undiluted phosphate buffer (pH 8.2-8.3) for 45 to 50 hours at 37° C. Immediately after treatment with trypsin the pieces were placed in absolute acetone and processed as described above. One of the scleroderma specimens submitted to the action of trypsin had its control portion fixed in formol saline with the usual alcohol dehydration instead of the acetone procedure described. Four scleroderma specimens did not receive treatment with trypsin.

Four pieces of normal skin were all kept in normal saline in the refrigerator for periods from 7 to 8 hours to 14 days and processed in the same fashion with or without trypsin treatment. Seven buffer controls were done: three scleroderma specimens and four normal specimens, the material being put into buffer solution alone and incubated for 45 to 48 hours at 37° C.

The specimens were cut at 5μ and the stains used were haematoxylin and eosin, Sheridan's modification of Weigert's elastic tissue stain, van Gieson, Heidenhain's modification of Mallory, the McManus reaction and meta-chromatic staining with toluidine blue with subsequent alcohol dehydration.

I should like to thank Dr. J. E. M. Wigley and Dr. J. O. Oliver for providing facilities for this research at the Institute of Dermatology; Dr. G. B. Dowling, Director of the Institute, for his constant encouragement and Mr. Lunnnon, Photographer to St. John's Hospital for Diseases of the Skin, London, for the photomicrographs. The work was done in conjunction with Dr. R. H. Seville and I am very grateful to him for his help.

REFERENCES

- GERSH, I., and CATCHPOLE, H. R. (1949) *Amer. J. Anat.*, **85**, 457.
HARKNESS, R. D., quoted by NEUBERGER, A. (1952) *Brit. med. Bull.*, **8**, 210.
HIGHBERGER, J. H., GROSS, J., and SCHMITT, F. (1951) *Proc. nat. Acad. Sci., Wash.*, **37**, 286.
MCMASTER, P. D., and PARSONS, R. J. (1950) *Ann. N.Y. Acad. Sci.*, **52**, 992.
PORTER, K. R. (1951) *Connect. Tissues*, 126.
TUNBRIDGE, R. E., TATTERSALL, R. N., HALL, D. A., ASTBURY, W. T., and REED, R. (1952) *Clin. Sci.*, **11**, 315.
WATSON, E. M., and PEARCE, R. H. (1950) *Ann. N.Y. Acad. Sci.*, **52**, 1004.
WYCKOFF, R. W. G. (1952) *Connect. Tissues*, 38.
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ACTH AND MELANIN PIGMENTATION.

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THE mechanism of melanin pigmentation has been studied extensively during recent years, but despite this a number of problems remain which require further examination. In the main, it is generally agreed that the skin pigment is formed by the action of the enzyme tyrosinase on the amino-acid tyrosine. For experimental purposes the free amino-acid is used, but in the skin it is possible that it is linked to a protein, the tyrosine groups of which become oxidized to melanin by the enzyme. It is also generally agreed that the enzyme is normally inhibited by sulphydryl substances and that before it can act it is necessary that these should themselves be oxidized, leaving free the prosthetic copper group of the tyrosinase which was hitherto united with the reduced sulphydryl. The main facts underlying this theory have been set out extensively in reviews by Lerner and Fitzpatrick (1950) and by Dowling and Whitlock (1952) and will not be discussed in detail here. Rothman and his colleagues (1946) and Flesch (1949) have shown that the sulphydryl content of skin is reduced by irradiation with ultraviolet light and it seems probable that other forms of radiant energy, such as heat and x-rays, act in the same manner. Similarly, one might explain the pigmentation induced by prolonged administration of arsenic as being due to the affinity of the metal for sulphydryl substances.

On the other hand, not all sulphydryl inhibitors produce pigmentation; Fitzpatrick (1952), who studied the effect of iodoacetamide and *p*-chloromercuribenzoic acid—both powerful inhibitors of sulphydryl groups—on skin tissue slices, was unable to demonstrate any release of tyrosinase activity after exposure of the tissue to these compounds. Another problem concerns the pigmentation of the nipples and genitalia induced by local application of oestrogens. If, as Figge and Allen (1941) suggested, this is due to increased oxidation of glutathione in the skin induced by the action of the oestrogen, one must offer some explanation why this action is confined to certain areas of the skin and not to the whole of it. In short, if sulphydryl inhibition of tyrosinase is to be accepted as the sole factor involved in the prevention of melanin pigmentation, these difficult facts must be adequately explained. There is, indeed, abundant evidence to show that sulphydryls play a very considerable part in the matter, but it seems equally certain that their rôle is not a simple one confined to the copper group in the tyrosinase.

When ACTH came into therapeutic use one of the more obvious side-effects observed was a marked melanosis of the skin similar to that seen in Addison's disease. It is thought that there is a reciprocal action between the pituitary and suprarenal glands which causes underproduction of adrenal steroids to be compensated by extra production of the adrenal-stimulating hormone of the pituitary, so leading to increased steroid formation; if the adrenal glands are destroyed by disease, there is a resulting over-production of ACTH. Thus the pigmentation seen in Addison's disease is of exactly the same type as that seen when ACTH is administered therapeutically.

This theory seems reasonable enough, but gives no account of the biochemical mechanisms involved. From the foregoing observations, one might expect the administration of ACTH to lead to increased inactivation of sulphhydryls and there is a considerable body of evidence to suggest that this does in fact take place. However, not all investigators are agreed about this and the precise action of ACTH on the tyrosinase-sulphhydryl complex has not been investigated.

Martini (1934) demonstrated a fall in the reduced glutathione in the blood of dogs after adrenalectomy, a finding which was confirmed by Ferrari (1935). Rivoire (1935) claimed that the administration of cysteine to cases of Addison's disease decreased the pigmentation and Leobardy and Labesse (1934) had also noted the same effect.

Blanchetière and Binst (1926) observed a fall in the blood glutathione in a patient suffering from Addison's disease. In the past there has been some evidence to suggest that treatment of this disorder with ascorbic acid will lessen the degree of pigmentation and it has long been thought that there is a deficiency of the vitamin in this disease. It seems that there has never been any convincing evidence to show that there is a definite fall in ascorbic acid levels in Addison's disease, but work to be mentioned later suggests that this might be so and that ACTH injections may lead to a similar fall. It is known that ascorbic acid is protected from oxidation by reduced glutathione, so that any stimulus which leads to increased oxidation of either substance will also lead to increased oxidation of the other. Therefore, if ACTH does lead to a reduction of the glutathione one might well expect a parallel fall of ascorbic acid at the same time.

Conn and his associates (1948) noted a fall in the blood glutathione in association with the development of hyperglycaemia when ACTH was administered. They also noted that those animals which resisted the diabetogenic effect of the hormone showed a smaller fall of the glutathione level. Later these workers, (1949) showed that the diabetogenic effect of ACTH when administered to normal men could be reversed if glutathione was given at the same time. Long, Miles and Perry (1951), having shown that tuberculin sensitivity in the guinea-pig could be reduced by ACTH and cortisone, found that the hormones had no effect if the guinea-pig was fed on a diet deficient in ascorbic acid.

They also noted that ascorbic acid reduced the tuberculin sensitivity but not if it was given as raw cabbage. Guinea-pigs on a cabbage diet were given injections of cortisone and ACTH and reduction in tuberculin sensitivity was then obtained. The effect of the cabbage diet could be simulated by an injection of glutathione. From these findings they deduced that there is in cabbage a factor which interferes with the desensitization produced by ascorbic acid, presumably by altering the metabolism of the vitamin. It is probable that this factor is a sulphydryl substance which protects ascorbic acid from oxidation, and the reversing action of the hormones could be explained by their lowering of the blood sulphydryl which would allow the ascorbic acid to be oxidized. It was later shown that the cabbage factor was ineffective in preventing desensitization by the hormones if dehydroascorbic acid was given at the same time. Alloxan, which is known to combine with sulphydryls, also reverses the action of the cabbage diet. It was found in addition that propyl thiouracil abolished the desensitising action of the ACTH and cortisone, and it is known that thiouracil and thiourea will inhibit tyrosinase in the same manner as does glutathione (Paschkis *et al.*, 1944; Bernheim and Bernheim, 1942).

Jarvinen (1951) showed that cortisone abolishes the erythema caused by ultraviolet light on the skin but that the subsequent pigmentation is more intense than usual. Ultraviolet light is known to inactivate sulphydryls *in vitro* and to reduce the skin sulphydryl content. The combined effect of light and hormone could be explained by postulating that cortisone lowers the sulphydryl content of the skin in addition to the normal action of ultraviolet irradiation, thus freeing tyrosinase from inhibition and leading to increased pigment formation. Hess and his associates (1951) have also noted a fall of blood glutathione levels in cases receiving ACTH.

All these findings seem to suggest that ACTH and cortisone lower the blood glutathione and, presumably, the glutathione content of the tissues. It must be said, however, that not all investigators are in agreement on this point and Joiner (1952) was not able to confirm any lowering of blood glutathione when ACTH was given.

The effects of ACTH and cortisone on ascorbic acid metabolism have also been studied. Stefanini and Rosenthal (1950) describe two patients under treatment with ACTH who developed symptoms of scurvy with a low plasma ascorbic acid level and who improved when the vitamin was given. One of the effects of ACTH is a sudden increase of urinary excretion of ascorbic acid followed by a fall. This phenomenon has been described by Beck and his colleagues (1950) who noted that it was not produced by cortisone. Dao and Shank (1951) find that patients under "stress"—major surgery—show a fall in plasma and urinary ascorbic acid with eosinopenia and increase of the urinary formaldehyde steroids, suggesting that these changes are the response to ACTH released by the pituitary reacting to the stress stimulus. Barker

and his colleagues (1950) noted low plasma ascorbic acid values with an initial high urinary output of the vitamin in animals receiving ACTH. Recent work by McSwiney and his associates (1954) demonstrated that in human and guinea-pig experiments ACTH causes an increased urinary excretion of ascorbic acid and also increased oxidation of the vitamin. These results were observed only in the presence of adequate saturation with ascorbic acid; they indicated that the vitamin could not originate solely by depletion of the suprarenal cortex but must also come from more general sources. Helve (1948) reported six patients suffering from Addison's disease who showed low serum ascorbic acid. In two of these cases the level was markedly diminished.

Whether these effects are the direct result of the ACTH stimulus or are secondary to a fall of sulphhydryl already described can not at present be decided. Nevertheless, it seems fairly certain, whatever the mechanism may be, that a fall of ascorbic acid would lead to a fall of glutathione, and that a fall of either would lead to increased melanogenesis since both are capable of inhibiting tyrosinase.

The action of the hormone on these mechanisms does not seem to have been studied extensively by *in vitro* experiments although Stewart *et al.* (1953) failed to show any effect of ACTH on ascorbic acid when incubated in the presence of blood plasma. It was in order to study the effect of ACTH on pigmentation and on the inhibiting mechanism that the following experiments were devised.

EXPERIMENT I.

For this experiment potato juice was used as the source of tyrosinase. A potato was peeled, scraped to a pulp, the juice strained off through muslin and centrifuged to remove the starch. Flat-bottomed conical flasks were used as containers and the reaction was carried out at room temperature. The buffer solution used was 1/15 M Sorensen phosphate buffer at pH 7.2. The contents of the flasks were made up as follows:

	Enzyme.	Glutathione.	ACTH.	Buffer.	Tyrosine.
A . .	0.5 c.c.	—	—	20 c.c.	5 mg.
B . .	0.5 „	2 mg.	—	20 „	5 „
C . .	0.5 „	2 „	2.5 mg.	20 „	5 „
D . .	0.5 „	2 „	5.0 „	20 „	5 „
E . .	0.5 „	2 „	10.0 „	20 „	5 „

In order to record the rate and time of colour change in the solutions they were examined at half-hourly intervals using a photoelectric colorimeter with a green filter. The results are shown graphically in Fig. 1.

This experiment was repeated a number of times and although there was slight variation in the figures obtained the ACTH consistently prolonged the period of inhibition of the tyrosinase. This was more marked with the greater amount of ACTH in flask E and the difference between flasks B and C was

usually too slight to be of significance. For simplicity the details of the control flask have been omitted but no colour change was observed when tyrosinase was allowed to act on ACTH alone without the addition of tyrosine, and ACTH did not inhibit or potentiate the action of tyrosinase in the absence of glutathione.

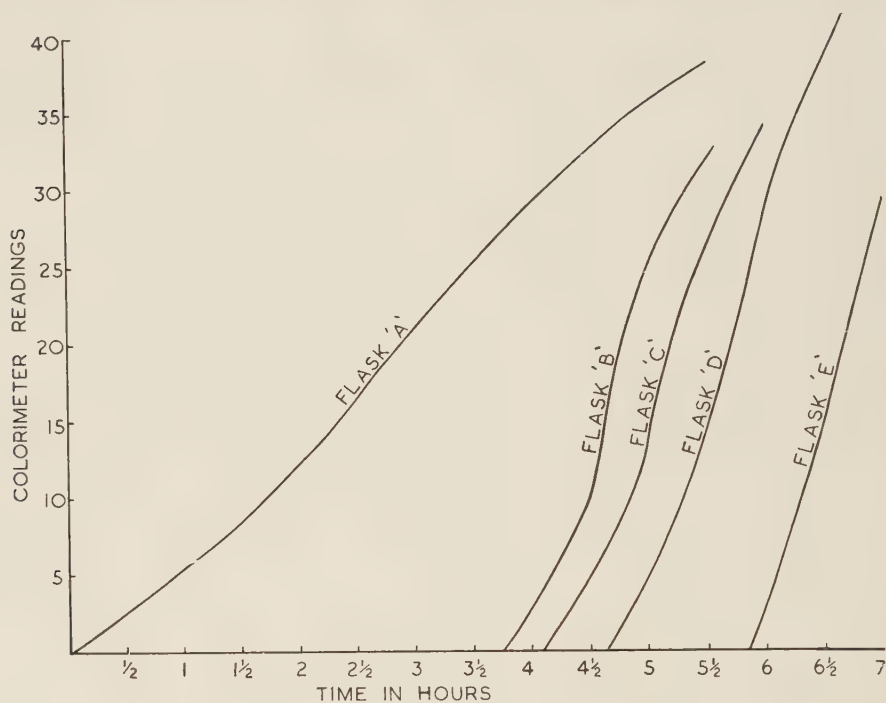


FIG. 1.

EXPERIMENT II.

The tyrosinase used in the first experiment was a crude preparation in which there were inert proteins, a large number of other enzymes and ascorbic acid. In order to determine the effect of ACTH on tyrosinase alone it was necessary to purify the latter to a certain degree.

For the initial experiments tyrosinase was purified from potato juice but as this gave a rather weak preparation it was decided to use mushrooms as the source and the tyrosinase was prepared as follows:

100 g. of mushrooms were pulped with 50 ml. of water, strained through muslin and centrifuged to remove debris. To the solution was added acetone to 37% by volume and the solution was centrifuged to remove the precipitate. To the supernatant more acetone was added to 70% by volume and the precipitate formed after centrifuging was taken up in 30 ml. of water. To this solution ammonium sulphate was added to half-saturation and the solution was allowed to stand in the cold for 2 hours. The precipitate which formed was removed by centrifuging and taken up in 20 ml. of cold water. This solution was used as the tyrosinase for the subsequent experiments where purified enzyme was required. It was tested and found to be free from peroxidase, catalase and cytochrome oxidase.

Flasks were prepared as in Experiment 1 but each flask contained 0.25 ml. of the enzyme solution and the inhibited flasks 0.5 mg. of glutathione as any larger amount prolonged the time of inhibition excessively. Measurements were made at half-hourly intervals as described in the first experiment.

RESULTS.

Flask B	containing	0.0 mg.	of ACTH,	inhibition released at	5 hours
" C	"	2.5	" " "	" " "	5 $\frac{1}{4}$ "
" D	"	5.0	" " "	" " "	7 "
" E	"	10.0	" " "	" " "	10 $\frac{1}{2}$ "

The result of the second experiment confirmed the less marked findings of the first and there seems no doubt that within the limits of the experiment the ACTH in some way protected the glutathione from oxidation. If small quantities 0.1 to 0.5 mg. of ascorbic acid were added to the inhibited flasks the inhibition was released earlier and the presence or absence of ACTH made no difference. The first experiment was repeated with the use of 5 mg. of ascorbic acid instead of glutathione as an inhibitor of the tyrosinase but all the inhibited flasks showed colour changes at the same time, indicating that the ACTH did not stimulate the oxidation of the vitamin either aerobically or by the enzyme ascorbic acid oxidase. The greater speed of oxidation of ascorbic acid as compared with glutathione and the protection of the vitamin from oxidation by the sulphhydryl which is then itself oxidised in the process would account for the shortening of the period of inhibition which results when ascorbic acid is added to the glutathione flasks.

The results of these experiments—the fact that ACTH prolonged the glutathione-induced inhibition of tyrosinase—were unexpected. In the living subject the evidence suggests that pigmentation caused by ACTH is associated with a fall in glutathione. The *in vitro* experiment produced an entirely opposite result. It seemed necessary, therefore, to consider whether the fall in the reduced sulphhydryl content *in vivo* might be brought about by the action of ACTH on some other biochemical system.

One of the observed effects when ACTH is given to human patients or experimental subjects is the development of a diabetic state with a diabetic type of blood-sugar curve. This seems to be associated with the fall in blood glutathione recorded by some observers and it is known that alloxan causes a fall of glutathione in association with the development of diabetes. Whether ACTH produces this effect directly or through the mediation of some other hormone is uncertain, but it seemed possible that it might act on one or more of the carbohydrate enzymes giving rise to a greater need for glutathione. It is known that many of these enzymes require the presence of reduced sulphhydryl for their efficient action (Barron and Singer, 1945).

In order to see whether any action of ACTH on carbohydrate metabolism could be detected leading to an increased demand for glutathione a number of preparations of carbohydrate enzymes were made and tested. Hexokinase was prepared from yeast by the method of Kunitz and Macdonald (1946), phosphorylase was prepared from potato by the method of Hanes (1940) and from

jack-bean meal by the method of Sumner and Somers (1947), and adenosine triphosphatase was prepared from potato by the method of Kalekar (1944). These enzymes were tested singly and in combination with their appropriate substrates but there was no evidence that ACTH promoted their use of reduced glutathione in such a way as to bring about an earlier release of tyrosinase inhibition. Finally an experiment was made to see whether ACTH would have any effect on the carbohydrate metabolism of live yeast in the presence of glucose and glutathione, but no evidence could be discovered of any increased utilization of the sulphydryl.

Thus, to sum up, the experiments so far described have shown that ACTH protects glutathione from oxidation, and that this action can be neutralized by the addition of small amounts of ascorbic acid; in the presence of carbohydrate enzymes ACTH does not produce any increased need for glutathione. Thus the theory that ACTH causes increased skin pigmentation by releasing tyrosinase from sulphydryl inhibition remains quite unconfirmed.

In the course of the experiments so far described it had been noted that the yield of tyrosinase from new potatoes was very much less than that obtained from older ones. As the tuber matures there must be new formation of the enzyme either by the production of a totally new copper-protein complex or by the addition of copper to a protein already present. It is known that it is possible to remove the copper from tyrosinase by dialysis so as to leave a protein which has no tyrosinase activity and that this activity can be restored by adding copper ions to the protein solution, although copper ions by themselves will not have any melanin-forming capacity when allowed to act on tyrosine.

In view of the negative findings so far described it seemed worth while to see whether ACTH has any effect on copper metabolism and whether it can increase the yield of tyrosinase when allowed to act on potato juice in the presence of copper.

EXPERIMENT III.

Four flasks were prepared as follows:

	Potato juice.	ACTH.	Ascorbic acid.
A . . .	10 ml. .	— .	—
B . . .	„ .	5 mg. .	—
C . . .	„ .	— .	5 mg.
D . . .	„ .	5 mg. .	5 mg.

Distilled water was added to each flask to bring the total contents to 12 ml.

The flasks were stoppered and incubated at 37° C. for 1½ hours. At the end of that time the tyrosinase in each flask was purified as follows:

Acetone was added to 37% by volume and the precipitate removed by centrifuging. To the supernatant fluid more acetone was added to 55% by volume, the solution was centrifuged and the precipitate obtained dissolved in 10 ml. of water.

Four more flasks were prepared, each containing 5 mg. of tyrosine and 20 ml. of phosphate buffer solution, pH 7.2. 2 ml. of each of the four enzyme solutions obtained

were added to the appropriate flasks and the rate of colour change recorded at half-hourly intervals using a photo-electric colorimeter with a green filter. The results are shown in Fig. 2.

This experiment seems to indicate quite clearly that ACTH increases enzyme yield under these experimental conditions and that the yield is greater if ascorbic acid is added. The vitamin possibly acts by maintaining the redox-

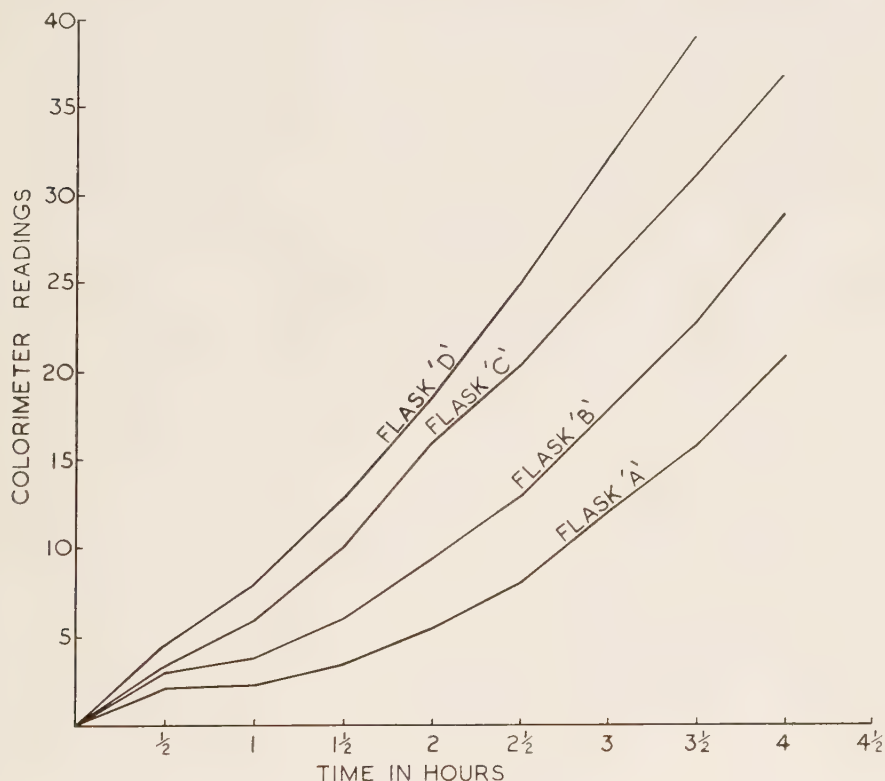


FIG. 2.

potential of the solution at the optimum for the formation of tyrosinase and one can but presume that the ACTH assists in keeping the ascorbic acid in the reduced state. Ascorbic acid would, of course, be present in the crude potato juice and the addition of the vitamin in small quantities merely accentuated the effects observed in flasks A and B. If ascorbic acid is added in larger quantities—20 mg. per flask—this action of ACTH is not observed, presumably because in the time allotted for incubation all the vitamin is not oxidized in either flask and so the protective action of ACTH is superfluous.

In this experiment additional copper was not added but considering the relationship between copper and ascorbic acid oxidation it seems highly

probable that copper entered into the reaction. The increased yields of tyrosinase recorded strongly suggest that this was due either to fresh formation of the copper protein or to some unmasking action of ACTH whereby the copper was activated. The next experiment was intended to show whether the addition of small amounts of copper solution to the substrate would increase the yield of enzyme.

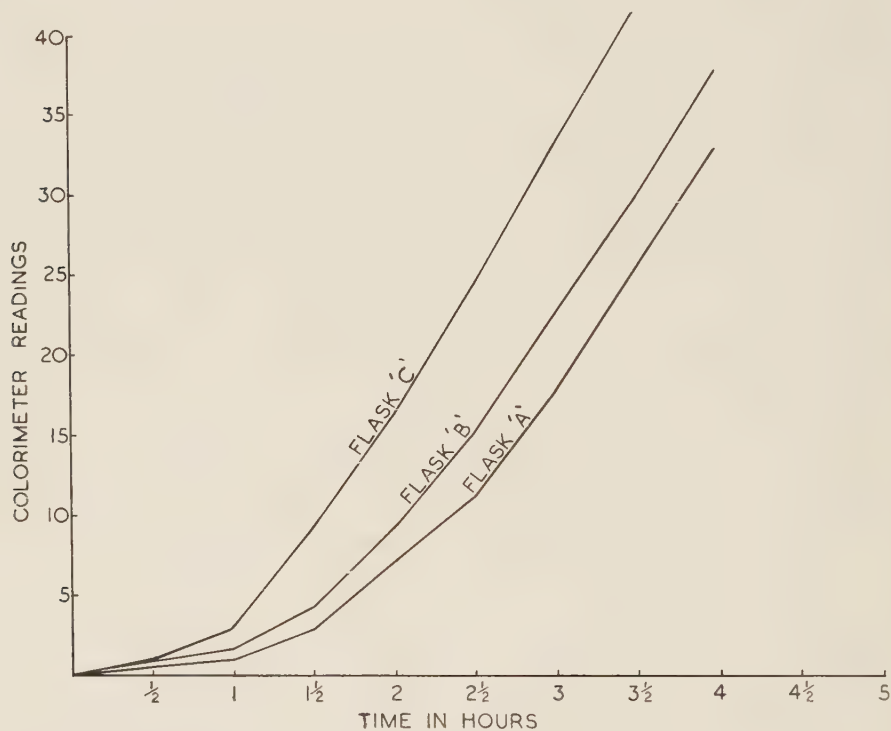


FIG. 3.

EXPERIMENT IV

Three flasks were prepared each containing 10 ml. of potato juice and 0.5 ml. of copper solution; this was prepared by dissolving 2 mg. of copper sulphate in one litre of distilled water, giving a concentration of 8×10^{-7} M of copper per ml. To flasks B and C were then added 5 mg. and 10 mg. of ACTH respectively, and the total contents of the flasks made up to 12.5 ml. They were incubated for $1\frac{1}{2}$ hours at 37° C.

As in the third experiment three flasks were now prepared containing 20 ml. of phosphate buffer at pH 7.2 and 5 mg. of tyrosine. To each flask was added 2 c.c. of the corresponding tyrosinase preparation. The results are shown graphically in Fig. 3.

This experiment shows that the presence of copper increases the yield of tyrosinase and that the yield is the greater with the larger quantity of ACTH. If the quantity of the copper solution was increased to 1.0 or 2.0 c.c. the differences between the flasks were not apparent, suggesting that in the presence

of an excess of copper ions the formation of tyrosinase would proceed to the maximum in each flask without the need of additional ACTH or ascorbic acid. There is of course only a certain quantity of protein available for the formation of the enzyme.

EXPERIMENT V.

It is known that glutathione will protect ascorbic acid from oxidation and from the earlier experiments it seemed that ACTH also protects glutathione. Ascorbic acid would be present in the potato juice so, on theoretical grounds, one should expect an enhanced yield of tyrosinase if glutathione were added to the flasks of juice before incubation.

Four flasks were prepared as follows :

	Potato juice.	Copper solution.	Glutathione.	ACTH.
A	10.0 ml.	0.5 ml.	—	—
B	10.0 „	0.5 „	—	5 mg.
C	10.0 „	0.5 „	7.5 mg.	—
D	10.0 „	0.5 „	7.5 mg.	5 mg.

The flasks were incubated for $1\frac{1}{2}$ hours and the tyrosinase purified from each flask as already described. To four other flasks containing the buffer-tyrosine solution was added 2 ml. of each of the corresponding tyrosinase preparations. The results are shown graphically in fig. 4.

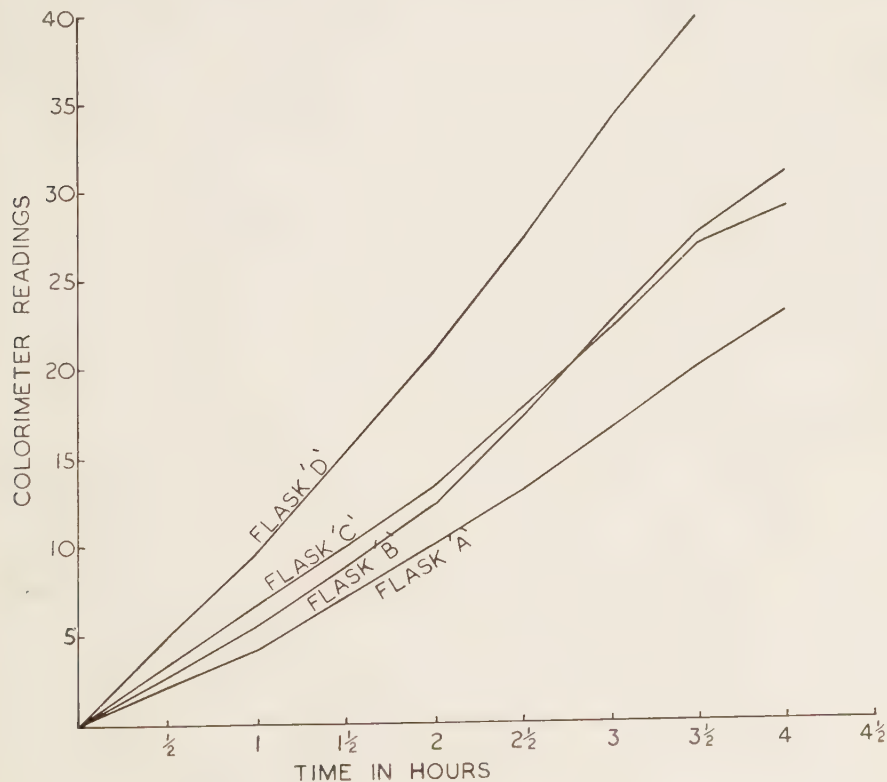


FIG. 4.

The difference in the readings between flasks B and C is insignificant suggesting that the glutathione protects the ascorbic acid in flask C to a degree corresponding to the protection given by ACTH in flask B. When both glutathione and ACTH are present the combined result is very much greater than when each substance is allowed to act singly owing to the additional protective action which the ACTH has on the sulphydryl.

If a greater amount of glutathione is added—15 mg.—to the flasks then the ACTH does not seem to have any effect on the yield of tyrosinase. Presumably in the time allotted for incubation all the glutathione is not oxidized so that the protective action of ACTH is superfluous. Similarly, if ascorbic acid is added as well as glutathione and ACTH no difference is observed between the flasks; the addition of the vitamin above that already present in the potato juice is then too great for the actions of the hormone or the sulphydryl to become apparent.

DISCUSSION.

To translate these results and findings into terms of human physiology is by no means a simple matter, and it must be admitted that there is no real reason why the one should closely correspond with the other. The experiments described isolate the reactions in a very artificial manner and take no account of the highly complex system of enzymes and other substances present in the melanin-forming cell in the skin. Certainly these experiments should be repeated with tyrosinase obtained from mammalian sources and, if possible, by *in vivo* experiments. In one respect these experiments are entirely contrary to findings obtained in human and animal subjects described in the earlier part of this paper. In these the bulk of the evidence suggests that ACTH causes a fall of both ascorbic acid and glutathione whereas in the experiments described here ACTH seems to protect them both from oxidation. There seems no reason to believe that the human and animal findings are in any way related to the pigment-forming action of the hormone and it is very likely that the action of ACTH on ascorbic acid depends very much on the organ in which it takes place. Very little is known about the action of ACTH on copper metabolism but it seems that it is here that we may find the answer to the question why ACTH causes skin pigmentation in the human subject when it is given therapeutically.

The observations of Rattner and his colleagues (1953) seem relevant to this matter. They found that administration of the melanocyte-stimulating hormone to rabbits caused a fall in serum copper and a decrease in the sulphydryl content of the skin. Whether or not this hormone is the same as ACTH is not entirely certain but Stebbins and Thomas (1953) were able to estimate the potency of ACTH preparations by its melanophore expanding properties in tadpoles, and it appears that present-day preparations of ACTH do contain the melanocyte-stimulating hormone even if the two are not identical.

One of the difficulties in connection with the modern theory of melanin pigmentation has already been mentioned in this paper—the fact that the application of sulphydryl-oxidising agents to the skin does not necessarily lead to

pigmentation as one would expect if the tyrosinase is inhibited by the presence of reduced glutathione. On the other hand, if it is accepted that tyrosinase can exist in the skin not only in an active form but also in a state where the protein part of the enzyme is not united to an active copper radicle, then there is no reason to expect that sulphydryl reagents would lead to increased pigmentation unless the tyrosinase has already been converted to an active form and is being prevented from acting by the presence of reduced sulphydryl. As far as these experiments are concerned it appears necessary for reduced ascorbic acid with or without reduced sulphydryl to be present before the copper group can unite with the enzyme protein. In consequence, the application of a sulphydryl-oxidizing agent to the skin would make this reaction less likely to occur rather than the reverse. Whether this conversion of pro-tyrosinase to the active enzyme requires a melanocyte-stimulating hormone for it to occur is by no means certain; but it certainly appears as if such a hormone stimulus greatly increases the speed of the reaction and yield of the enzyme.

It is tempting to apply this hypothesis to some of the problems of pigmentation met in clinical practice. In vitiligo there is a total absence of pigment formation within the affected area. There is no evidence that this is due to excess of sulphydryl inhibitors of the enzyme and the application of sulphydryl-oxidizing agents to the depigmented skin or exposure to actinic rays do not lead to pigment formation. One can assume either that the enzyme required for pigment formation is absent or, I suggest, that the enzyme is present but in an inactive state requiring the addition of copper for its activity to become apparent. It would not be unduly difficult to devise an experiment to test this theory and to see whether ACTH with or without the addition of copper and ascorbic acid could bring about a return of pigment in an area of vitiligo.

Certain inflammatory dermatoses lead to marked increase of skin pigmentation whereas others, with apparently the same degree of severity of inflammation, do not. Exfoliative dermatitis, pemphigus, disseminated lupus erythematosus, dermatitis herpetiformis and lichen planus either when they recover or during the course of the disease themselves all lead to marked melanosis of the affected skin. A dermatitis due to an external sensitizing agent, an ordinary eczema or the so-called seborrhoeic eczema may set up an extensive and prolonged inflammation of the skin but it is not usual for them to be followed by a pigmentation comparable in degree with that which follows the dermatoses previously mentioned. It is held nowadays that certain dermatoses are the result of exposure to stress and those of the first group mentioned above as causing much pigmentation are included among the stress diseases. Stress is said to lead to increased production of ACTH; if that is so one might well expect these dermatoses to be followed by increased pigmentation whereas those in which the stress element is slight would not lead to such a degree of melanin formation.

One of the problems connected with skin pigmentation concerns the latent interval which occurs between exposure of the skin to ultraviolet light and the development of pigment. If the action of light is to oxidize the reduced sulphydryls present in the skin and which are inhibiting tyrosinase one would expect an immediate production of melanin once this inhibition has been removed. But this is not the case; it is a matter of days before pigmentation develops after the ultraviolet light stimulus. However, if this latent interval is occupied by the formation of active tyrosinase from an inactive precursor, then one would expect time to pass before pigmentation became visible.

It must be emphasized that these explanations should be regarded as only hypotheses and not as proven facts; a great deal of work needs to be done before some of the inconsistencies mentioned in this paper are resolved, but a working hypothesis may be of value even if it is later found to be incorrect. The experiments recorded in this paper were done with tyrosinase obtained from non-mammalian sources and carried out in the highly selective environment of a test-tube. Within the limits of the experiments it was not possible to show the effects of ACTH on the carbohydrate enzymes, although it is known that ACTH considerably influences their action. Carbohydrate metabolism may well be connected with the utilization of sulphydryl substances and is perhaps of greater importance in pigment formation than the action of ACTH on copper metabolism or on the sulphydryl preserving effects described here.

SUMMARY.

- (i) The effects of ACTH on glutathione and ascorbic acid metabolism in animal experiments and human therapeutics are briefly reviewed.
- (ii) Experiments are described in which it was found that ACTH retarded the rate of release of inhibition of tyrosinase when glutathione was used as the inhibiting agent. The addition of ascorbic acid neutralized this sulphydryl-preserving effect.
- (iii) Further experiments are described in which ACTH was incubated with potato juice with the addition of copper, glutathione and ascorbic acid. The ACTH was shown to increase the yield of tyrosinase in these experiments.
- (iv) It is suggested that tyrosinase can exist in the skin in an active and an inactive form. Some of the implications of this theory are discussed with particular reference to certain of the pigimentary dermatoses.

I am extremely grateful to Armour Laboratories Ltd. for a most generous gift of ACTH; to the Research Sub-committee of the South-Western Regional Hospital Board for a supply of ACTH and to their encouragement to me to carry out this investigation; and to Roche Products Ltd. for a gift of pure ascorbic acid.

REFERENCES.

- BARRON, E. S. G., and SINGER, T. P. (1945) *J. biol. Chem.*, **157**, 221.
- BECK, J. C., ENGLISH, M. M., HACKNEY, J. W., and MACKENZIE, K. R. (1950) *J. clin. Invest.*, **29**, 798.
- BERNHEIM, F., and BERNHEIM, M. L. C. (1942) *J. biol. Chem.*, **145**, 213.
- BLANCHETIÈRE, A., and BINST, L. (1926) *C.R. Soc. Biol., Paris*, **95**, 1028.
- BOOKER, W. M., HAYES, R. L., and DENT, F. M. (1950) *Fed. Proc.*, **9**, 14.
- CONN, J. W., LOUIS, L. H., and JOHNSTON, M. W. (1948) *Proc. Amer. Diabetes Ass.*, **8**, 215.
- (1949) *Science*, **109**, 279.
- DAO, T. L., and SHANK, R. E. (1951) *J. Lab. clin. Med.*, **38**, 802.
- DOWLING, G. B., and WHITLOCK, F. A. (1952) *Practitioner*, **168**, 453.
- FERRARI, R. (1935) *Arch. Fisiol.*, **34**, 364.
- FIGGE, F. H. J., and ALLEN, E. (1941) *Endocrinology*, **29**, 262.
- FITZPATRICK, T. B. (1952) *Arch. Derm. Syph., Chicago*, **65**, 379.
- FLESCH, P. (1949) *Proc. Soc. exp. Biol., N.Y.*, **70**, 136.
- HANES, C. S. (1940) *Proc. roy. Soc. B.*, **129**, 174.
- HELVE, O., Quoted by SIMPSON, S. L. (1948) *Med. Annu.*, p. 13.
- HESS, W. C., KYLE, L. H., and DOOLAN, P. D. (1951) *Proc. Soc. exp. Biol., N.Y.*, **76**, 418.
- JÄRVINEN, K. A. J. (1951) *Brit. med. J.*, ii, 1377.
- JOINER, C. L. (1952) *Ibid.*, ii, 642.
- KALCKAR, H. M. (1944) *J. biol. Chem.*, **153**, 355.
- KUNITZ, M., and McDONALD, M. R. (1946) *J. gen. Physiol.*, **29**, 143.
- LÉOBARDY, J. DE, and LABESSE, A. (1934) *Pr. méd.*, **42**, 599.
- LENER, A. B., and FITZPATRICK, T. B. (1950) *Physiol. Rev.*, **30**, 91.
- LONG, D. A., MILES, A. A., and PERRY, W. L. M. (1951) *Lancet*, i, 1085.
- (1951) *Ibid.*, i, 1392.
- (1951) *Ibid.*, ii, 902.
- McSWINEY, R. R., CLAYTON, B. E., and PRUNTY, F. T. G. (1954) *Ibid.*, i, 178.
- MARTINI, V. (1934) *Arch. Fisiol.*, **33**, 175.
- PASCHKIS, K. E., CANTAROW, A., HART, W. M., and RAKOFF, A. E. (1944) *Proc. Soc. exp. Biol., N.Y.*, **57**, 37.
- RATTNER, W. H., LERNER, A. B., and FITZPATRICK, T. B. (1953) Unpublished: quoted by LERNER (1953) in *Advanc. Enzymol.*, **14**, 91.
- RIVOIRE, R. (1935) *Pr. méd.*, **43**, 1122.
- ROTHMAN, S., KRYSA, H. F., and SMILJANIC, A. M. (1946) *Proc. Soc. exp. Biol., N.Y.*, **62**, 208.
- STEBBINS, R. B., and THOMAS, G. B. (1953) *Ibid.*, **84**, 44.
- STEFANINI, M., and ROSENTHAL, M. C. (1950) *Ibid.*, **75**, 806.
- STEWART, C. P., HORN, D. B., and ROBSON, J. S. (1953) *Biochem. J.*, **53**, 254.
- SUMNER, J. B., and SOMERS, G. F. (1947) *Chemistry and Methods of Enzymes*. 2nd ed. New York, N.Y.: Academic Press Inc.

RUDIMENTARY POLYDACTYLY.*

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RUDIMENTARY supernumerary fingers may present as small, wart-like tumours of the hand. Such cases are occasionally referred to dermatologists, to whom they seem to be less familiar than to paediatricians and surgeons. As there appears to be little reference to these structures in the dermatological literature, a record of five illustrative cases may be of interest.

CASE REPORTS.

CASE 1.—A Yoruba man of 21. A bullet-shaped tumour has been present on the ulnar border of the right hand since birth (Fig. 1). It was attached to the base of the little finger and measured 1 cm. in length and 0.5 cm. in diameter at its attachment. It was rubbery in consistency and had a polished, horny surface. The patient stated that this was a common condition in his race and that other male members of his family had had similar things removed shortly after birth. The lesion was excised.

Histologically it showed an acanthotic and hyperkeratotic epidermis overlying a conical dermal spur (Fig. 2). This contained many blood vessels and nerve bundles. Numerous Wagner-Meissner bodies were visible in the dermal papillae, even in the tip of the lesion. No hair follicles, sebaceous glands, bone or cartilage were found. Sweat ducts and glands were present in the base of the structure.

CASE 2.—A male Cypriot aged 28. A small mass had been present on the ulnar side of the proximal phalanx of the right little finger since birth. It measured about 0.5 cm. in length and was attached by a slightly constricted peduncle. In the accompanying Fig. 3, a triradius can be detected. No family history was obtained.

On histological examination, it showed a fibrous core with numerous blood vessels, nerve bundles and laminated nerve endings of both Wagner-Meissner and Vater-Pacini type. No epidermal appendages or skeletal elements were present. The epidermis was acanthotic and hyperkeratotic over the top of the lesion and flattened and parakeratotic at the sides (Fig. 4).

CASE 3.—A girl of 7. A small tag at the base of the left little finger was noticed at birth and an unsuccessful attempt was made to remove it with a ligature. It had grown into a narrow fleshy structure about 0.5 cm. in length. She was an adopted child. Her foster mother stated that similar lesions were common in the mother's family, but apart from this, no family history was obtainable.

Histologically, the epidermis was hyperkeratotic. The dermal component contained many blood vessels and bundles of nerve fibres. Wagner-Meissner corpuscles were again profuse.

CASE 4.—A woman aged 30. Symmetrical wart-like lesions had been present since birth on the ulnar aspects of the hands at the bases of the little fingers. They measured about 0.5 cm. in diameter and were raised a few millimetres from the surface

* Based on a paper read at the Thirty-fourth Annual Meeting of the British Association of Dermatology, June, 1954.

of the hand. There was no family history of such lesions or of other forms of polydactyly.

Histologically, one of the lesions showed acanthosis and hyperkeratosis of the epidermis. In the dermis there was a concentration of nerve bundles. Wagner-Meissner bodies were numerous in the dermal papillae.

CASE 5.—A girl aged 5. A unilateral, sessile, warty growth had been present on the ulnar border of the base of the little finger since birth. Her father was similarly



FIG. 1.

affected and a paternal uncle had had a more extensive supernumerary finger. Her mother and two sisters were normal.

Histologically, the lesion closely resembled that in Case 4: Vater-Pacini corpuscles were present.

DISCUSSION.

Polydactyly is not uncommon and its grosser forms are self-evident. The extra digit may separate proximally from the carpus or tarsus, and in the hand

may have its own metacarpal bone. If the separation is more distal no extra metacarpal is found, but the extra finger arises at the base of a normal one. If the separation is even more distal, the supernumerary finger arises from the surface of a normal finger.



FIG. 2.



FIG. 3.

According to most authorities, the postaxial position is relatively more common in polydactyly of the hand, i.e., the extra finger occurs towards the ulnar side of the median axis. Commonly, it arises on the ulnar border of the hand, at the base of the little finger or thereabouts.

Although the extra finger may be perfectly formed, it is frequently incomplete. At times, a supernumerary finger is attached by a narrow flap or cord of soft tissue to the ulnar surface of the hand. When the extra finger is more primitive, a soft blob of tissue, perhaps bearing a nail or containing a tiny mass of cartilage, is attached in the same way. Such a mass was at one time called

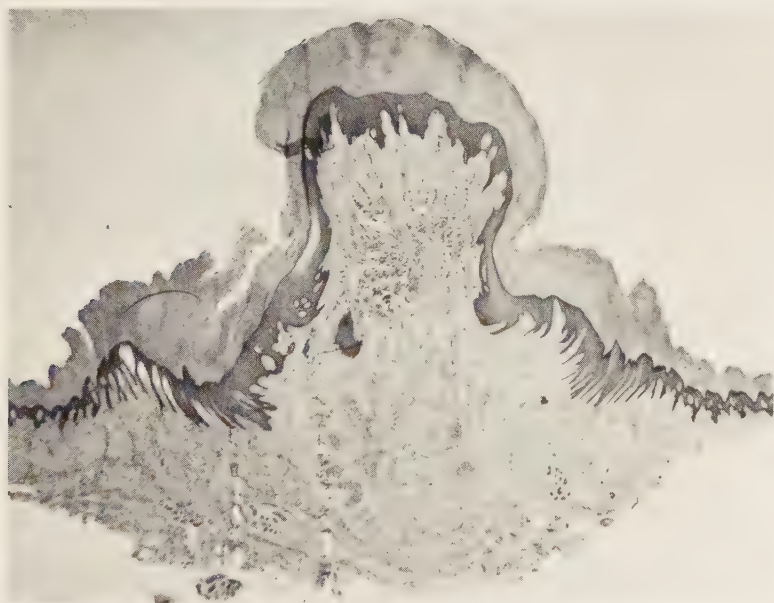


FIG. 4.

a "fibroma pendulum digiti quinti" (Annandale, 1865) but when it became apparent that it was a rudimentary supernumerary finger, it became known as a "pedunculated postminimus".

An even more rudimentary form consists of small tumours of the type described above. Lewis (1912) included this form in his classification of polydactyly, referring to it as a small skin-clad nodule. Bonnevie (1919) studied the genetics of asymmetrical rudimentary polydactyly and concluded that the condition was inherited as a dominant, but that cases were missed because at times it showed merely as a small soft knob at the side of the hand. Ruggles Gates (1946) stated that the most common type of polydactyly in the American negro was the pedunculated postminimus, more extreme reduction showing as

a slight excrescence at the site where supernumerary digits were commonly encountered.

Cummins (1932) described the pedunculated form in 56 cases. A family history of the condition was obtained in 15. His studies were largely concerned with the theory that pedunculation is due to intrauterine strangulation by amniotic bands.

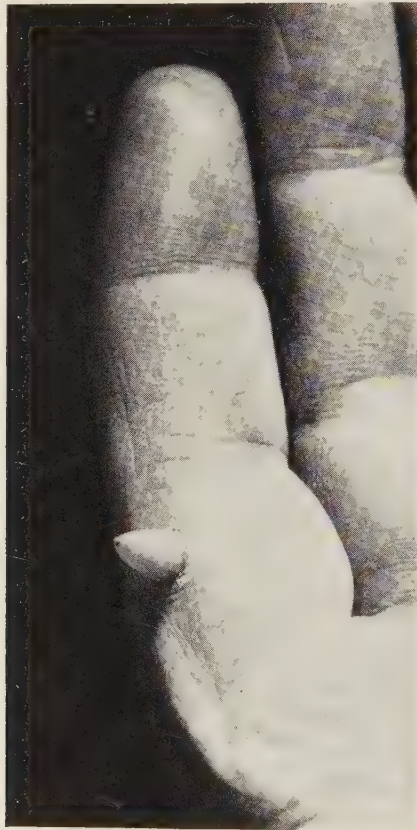


FIG. 5.

This theory has been used to explain congenital constrictions in digits or limbs or their congenital absence. Cummins found no evidence of such strangulation in pedunculated postminimi and he restated the problem by quoting Streeter's (1930) opinion that pedunculation occurred because of an inherent incapacity of the affected region to grow. He made the suggestion, however, that some of the small, sessile forms of polydactyly might represent the amputation stumps of pedunculated postminimi which had gone a stage farther and fallen off. He described the histology of pedunculated postminimi and pointed

out the abundance of nerves and nerve endings. The absence of hair follicles and sebaceous glands he did not consider anomalous since he thought that the postminimus was equivalent to the terminal and penultimate phalanges of a normal finger in "integumentary potencies". (Kanavel, 1932, stated that in simple hypophalangism the absence was nearly always of the middle phalanx.)

Cummins and Midlo (1943) have elsewhere described how dermoglyphics, i.e., dermal ridge markings, can be used to identify a dubious structure as a rudimentary digit. A Y-shaped confluence of dermal ridges, called a triradius, occurs at the base of all normal digits and may be expected near a



FIG. 6.

supernumerary one (Fig. 3). An amputated lesion may or may not show continuation of the dermal ridges over the surface, depending on whether the extra structure was lost before ridge differentiation or after. Normal fingers separate from the hand plate by the eighth week of intrauterine life and ridge differentiation occurs at the third and fourth foetal months.

The cases reported here are similar to one another in being congenital and in three cases familial. All occurred in the neighbourhood of the base of the little finger where extra fingers are common and in one a definite triradius was seen. The histology was consistent with a diagnosis of supernumerary digit, resembling that of pedunculated postminimi in the presence of numerous nerves and nerve endings and the absence of hairs and sebaceous glands. The history

and histology did not suggest that they were simple fibromas, although these may present as finger buds (Mawson, 1953).

They showed a superficial resemblance to fibrokeratomas such as von Roll's case described by Moncorps (1931) as a "false cutaneous horn". A similar lesion is shown in Fig. 5. It consisted of a horny growth about 1 cm. in length arising abruptly from the flexor surface of the proximal phalanx of the left index finger in a man aged fifty. It had begun a year before as a "little wart" which bled on pressure. Histologically, also, it showed a certain resemblance to the lesion in Case 1, being composed of a conical mass of fibrous tissue bearing a markedly acanthotic and hyperkeratotic epidermal layer. Nerve fibres and laminated nerve endings were absent (Fig. 6).

SUMMARY.

Supernumerary fingers may present as small wart-like growths. The clinical and histological features of five cases are described.

I am indebted to the following for material and permission to publish: Dr. W. N. Goldsmith (Case 1); Mr. L. W. Plewes (Case 2); Dr. I. Martin-Scott (Case 3); Dr. H. J. H. Wallace (Case 4); Dr. O. L. S. Scott (Case 5). I am also grateful to Prof. L. S. Penrose for information on dermoglyphics and to Dr. Julia Bell for her interest in these cases.

REFERENCES.

- ANNANDALE, T. (1865) *The Malformations, Diseases and Injuries of the Fingers and Toes*. Edinburgh: Edmonston and Douglas.
- BONNEVIE, K. (1919) *Norsk. Mag. Laegevidensk.*, **80**, 601.
- CUMMINS, H. (1932) *Amer. J. Anat.*, **51**, 381.
- and MIDLO, C. (1943) *Finger Prints, Palms and Soles*. Philadelphia: The Blakiston Company.
- GATES, R. R. (1949) *Pedigrees of Negro Families*. Philadelphia: The Blakiston Company.
- KANAVAL, A. B. (1932) *Arch. Surg.*, **25**, 283.
- LEWIS, T. (1912) *Treas. hum. Inherit.*, **1**, 6.
- MAWSON, R. (1953) *Brit. med. J.*, **i**, 1149.
- MONCORPS, C. (1931) in Jadassohn's *Handbuch der Haut- und Geschlechtskrankheiten*, **8/2**. Berlin: Springer.
- STREETER, G. L. (1930) *Contr. Embryol. Carneg. Instn.*, 126.

FAVUS OF SCALP WITH UNUSUAL EPIDEMIOLOGICAL FEATURES.

PETER INMAN.

Consultant Dermatologist, Sunderland and West Hartlepool.

Case Report.

A WOMAN, aged 49, inmate of an institution for mental defectives. She was first seen in the department of dermatology in October, 1952. At that time she had a localized area of cicatricial alopecia in the right posterior parietal region. There was a good deal of crusting and scaling over this patch, and some of the isolated crusts at the margin were about the size of a sixpence. The long unbroken hairs in the neighbourhood of the patch fluoresced green under Wood's light.

The skin of the body and limbs was normal, and the nails were healthy. The clinical diagnosis of favus was considered likely. Cultures grew *Trichophyton* (achorion) *schonleini*.

The patient had been an inmate of the institution since 1936. She never left the institution except for an occasional escorted visit to the cinema and one monthly visit to her widower father. A nursing sister of the institution remembered clearly the admission of the patient in 1936, and said that the bald area was present at that time. Moreover, the sister is convinced that the bald patch persisted unchanged during the intervening years. It seems, therefore, that the patient is an astonishing example of a case of scalp favus with no material spread over a period of sixteen years.

In view of the difficulty there might be in getting a mental defective to hold still for x-ray epilation it was decided to use Whitfield's ointment only and to observe the case. With regular rubbing in of the ointment twice daily by the attendant there was a steady and quite remarkable spread of the disease over the scalp such as had not occurred in sixteen years of untreated infection. It appeared that the rubbing had merely spread the organism and that the fungicide was without any effect.

The number of inmates in the institution varies between 150 and 160. In March 1953 the scalps of all these patients were inspected clinically and under Wood's light. A few patients had scaling of the scalp and any suspicious areas were cultured. No case of fungous disease was discovered. Thirteen months later, in April, 1954, the scalps of the entire colony were again carefully scrutinized clinically and under Wood's light and again no case of favus was revealed.

In June 1953 six cases of a ringed eruption about the neck and limbs occurred in other inmates of the home. Of these six, two were cultured and both grew *Trichophyton* (achorion) *schonleini*. These lesions healed quickly with the application of Whitfield's ointment. Careful watch was kept, but no other lesions appeared in any of the patients until eleven months later. In May 1954 there was a sudden shower of twelve similar cases of a ringed eruption

on the limbs and neck. Of these twelve cases eight were cultured; of the eight cultures, seven grew no fungus, but the eighth grew *Trichophyton (achorion) schonleini*.

These two showers of contact cases at eleven months' interval are difficult to explain. It is true that the patient with scalp favus worked as a kitchen maid; in this privileged position the payment of visits by other inmates for the purpose of obtaining "cookies" is apparently not unknown in the institution. However, she had worked in the kitchen for some years and there is no obvious reason why contact cases should occur in a number of patients at the same time. The dormitory accommodation has been inspected, but the contact cases were fairly evenly distributed throughout all the dormitories and the sleeping arrangements do not seem to afford any explanation of the secondary cases.

The patient's scalp was epilated with x-rays in July 1954.

SUMMARY.

A case of scalp favus is described in an inmate of a mental defective home housing between 150 and 160 patients. For seventeen years no contact case of favus occurred in the other inmates although there is strong evidence that the patient suffered from scalp favus during this period. Two outbreaks of contact cases affecting the glabrous skin only occurred in the eighteenth year. It seems that the rubbing in of fungicidal ointment was responsible for the production of these contact cases as well as for the spread of the disease on the original patient's scalp.

I am indebted to Dr. J. Walker of the London School of Hygiene and Tropical Medicine for all the cultures in this investigation.

ROYAL SOCIETY OF MEDICINE.

SECTION OF DERMATOLOGY.

President—Dr. R. T. BRAIN.

21 January 1954.

Xanthomatosis.—Dr. R. M. B. MACKENNA and Dr. C. D. CALNAN.

Dr. CALNAN : This is a Cypriot girl aged 19 years who since the age of 5 has had the present skin lesions which have progressively become worse. She has been investigated in the Middlesex Hospital under the care of Professor A. Kekwick. She has no symptoms of heart disease. One sister has been examined and her cholesterol level was normal. Another sister is said to have xanthomatous lesions. Our patient has gross lesions of xanthoma tuberosum on her elbows, knuckles, knees, and over the spine. On the arms, buttocks, breasts, shoulders and legs are sheets of xanthoma planum showing as aggregated orange-yellow papules with a pale dusky erythematous background. The palms and soles are normal. Liver and spleen are not palpable. There is a loud systolic murmur and thrill at the base of the heart with an accentuated aortic second sound. B.P. 130/80. Fundi normal.

Serum cholesterol has varied from 800 mg.% to 2000 mg.%. The serum is not lipaemic. Plasma proteins show increased β -globulin. Treatment : heparin 25,000 units twice a week for 2 months without benefit.

Dr. A. D. PORTER : I have treated two patients with heparin, beginning with 25 mg. and increasing the dose over a period of three months. In one the blood cholesterol rose steadily while under treatment until it was 100% higher than at the beginning ; in the other the blood cholesterol remained almost stationary.

Trichophyton Rubrum Infection.—Dr. R. M. B. MACKENNA and Dr. C. D. CALNAN.

A girl aged 18 who for four years has had scaling on the soles and between the toe webs with discoloration of the toenails. Three years ago the palmar surface of the right hand and fingers became thickened and scaly. About the same time a scaly patch appeared on the lower part of the left leg. Both feet show scaling over the soles and sides, with maceration in the interdigital spaces ; there is some spread on to the dorsum of the foot. All the toenails are thickened and discoloured.

On the left leg there is a large irregular patch of erythema with scattered follicular papules and pustules. On the right hand the palmar surface is hyperkeratotic and scaly, especially in the creases. The finger nails are dystrophic.

Scrapings from soles, toe webs, left leg, right palm, and finger and toe nails all contain fungus. Culture : *T. rubrum*. Lanugo hairs from patch on left leg contain fungus—a large spored endothrix.

Dr. PORTER : I have had two rather similar examples. One of them was diagnosed and had been treated as Bazin's disease for several years. The other was similar. Both were women and both had nodules in the skin. A feature that struck me was the exacerbation during the summer months. In one of them the nails of the toes were affected also. It may be as Dr. Calnan has suggested that the hairs on the limbs contained a fungus.

Dr. FINDLAY : May I just mention some work on the Continent ? Dr. CREMER in Amsterdam has written a paper recently on this same problem of patients who are typical candidates for

Bazin's disease. They are usually young women with the typical appearance on the extremities and they have this particular nodular type of reaction around the site of infection. The point is not so well recognized in this country. They are diagnosed either as erythema nodosum or Bazin's disease.

CREMER, G. (1953) *Dermatologica*, **107**, 28.

Acne Agminata.—Dr. R. H. MEARA.

A. R.—, draughtsman, aged 35.

History.—Eleven months ago an eruption appeared on the face quite suddenly without symptoms. Since that time there has been little change except that more lesions have appeared, particularly about the eyelids. No drugs were being taken at the onset of this condition and there is no history of previous illness.

On examination.—About the central area of the face, particularly the eyelids and chin, are many small brownish red papules; some of these show central pustule formation. On diascopy they leave faintly brown translucent spots.

Investigations.—(1) The patient has had a routine skiagram of the chest every year for five years. The last picture, taken in September 1953, showed no evidence of disease.

(2) E.S.R. [Westergren]; 2 mm. in 1 hour.

(3) Mantoux reaction, 1/10,000: positive.

(4) Biopsy of a lesion of left side of the chin (17 June 1953); the histological report by Dr. H. Haber was as follows:

"The epidermis shows some plugged follicles. In the dermis there is vascular engorgement and patchy areas of round cell infiltration. Many of these areas are perifollicular and show some endothelial and giant cells. A specific aetiology has to be considered."

Response to treatment.—For eleven weeks he was given isonicotinic acid hydrazide alone (100 mg. *t.d.s.*) and then for the next eight weeks together with injections of streptomycin 1 g. twice weekly. During the period of treatment his condition steadily became worse.

I wish to thank Dr. G. B. Mitchell-Heggs for kindly permitting me to present this patient.

Dr. F. RAY BETTLEY: There appeared in this case to be an excessive number of giant cells, a recognized feature of this disease. I agree that there is no good evidence that this is tuberculous.

Pre-mycosis.—Dr. STEPHEN GOLD.

The patient, a woman aged 39, has noticed the present eruption for the past five years. She says that it comes and goes, but has never been completely clear during that time. She has noticed moderate irritation. On examination there is a widespread scaly eruption of the parapsoriasis-en-plaque variety scattered over the trunk and limbs. When first seen, there were three umbilicated pustules the size of a pea, grouped on her left shoulder. She has noticed this type of lesion from time to time; they tend to develop central necrosis and leave a small scar. To-day there is a small scabbed area remaining from one of these pustules on her abdomen. Both breasts show a reticulate poikilodermatous eruption.

Investigations.—Complete medical examination has revealed no abnormality apart from the skin eruption. There is no glandular enlargement. The liver and spleen are not palpably enlarged. Complete blood count reveals no anaemia. Total W.B.C. 6000 per c.mm. (Normal differential). Bone marrow; specimen virtually normal. No evidence of leukaemia. The percentages of reticulum cells and eosinophils are not significantly increased. Skin biopsy: The corium is heavily infiltrated with rounded cells. Many of the nuclei are bizarre. Mitoses are frequent and a few multinucleated giant cell forms are present. This is a dermal reticulosis showing

the combination of nodules, parapsoriasis en plaque and poikilodermatous changes at the same time.

Dr. H. HABER: Civatte recognizes now only two types of parapsoriasis as belonging to this group: Parapsoriasis en plaque and parapsoriasis lichenoides. Transitions between the two groups can be observed. Both groups may show papules providing a common link between parapsoriasis en plaque and parapsoriasis lichenoides.

The papules are due to dense collections of round cells. The papules in pityriasis lichenoides chronica are of epidermal origin and heal within three weeks. The papules in the true parapsoriasis group last indefinitely. Pityriasis lichenoides chronica is an entity by itself and must be separated from true parapsoriasis. Dr. Gold's case shows parapsoriasis en plaque and papules. Histologically these papules are composed of round cells and there is a tendency of the infiltration to spread. We are dealing most probably with a case of parapsoriasis en plaque with papules with early mycosis fungoides change.

REFERENCE.

CIVATTE, A. (1951) *Ann. Derm. Syph.*, **78**, 5.

The following cases have been published in *Proc. R. Soc. Med.*, **47**, 404:

Exfoliative Dermatitis with Lymphatic Leukaemia.—Dr. J. FIELDING and Dr. H. T. H. WILSON.

Sezary's Erythrodermia.—Dr. J. FIELDING and Dr. H. T. H. WILSON.

Arsenical Keratoses and Epithelioma with Bronchial Carcinoma.—Dr. C. D. CALNAN.

The following cases also were shown:

Case for Diagnosis. ? Chronic Lymphatic Obstruction Following Injury.—Dr. BETHEL SOLOMONS, Jr.

Cutaneous Leishmaniasis.—Dr. R. H. MEARA.

BOOK REVIEW.

DETERGENTS.*

THE author divides his book into three main parts : In the first he compares the characteristics of soaps and synthetic detergents and emphasizes the role of the latter in colloidal systems and particularly in connection with the formation of gels. The second deals with the problems and difficulties relating to the biological adsorption of various locally applied substances and the tremendous variations in skin permeability depending on many factors, both internal and external ; in general terms, he reviews the problems of sensitization and anaphylaxis and reference is made to the similar properties of known carcinogenic agents and the synthetic detergents. The third deals with the use of these products in personal and general hygiene ; the necessity for rinsing is stressed. Mention is made of their use in cosmetics, shampoos and dentifrices, and in industry—in the mines, food processing, insecticides and fire extinguishers. Their importance in increasing the permeability of the skin to dyes is emphasized with the increased likelihood of sensitization. He suggests the theoretical possibility that by some physico-chemical process the normal cellular rhythm may be altered with incitement to “*neoformation*”. All these new synthetics should be subjected to careful biological study in every case before being used for human hygiene.

Clinicians will find this book rather disappointing, as it seems to be a compilation of a mass of poorly diagnosed material uncritically presented. The author's concepts of the pathological effects of detergents are highly imaginative.

J. B. L.

* *Les Détersifs En Hygiène et Cosmétique*. By W. KOPACZEWSKI. (1954) Paris : Masson et Cie. Pp. 152. Illus. 14. Price 1800 fr.

CURRENT LITERATURE.

PENETRATION OF RADIOACTIVE STEARIC ACID INTO THE SKIN OF THE RAT. E. O. BUTCHER. (1953) *J. invest. Derm.*, **21**, 243.

The addition of iodine depolymerizes linoleic acid so that the ultimate chemical effect is that of monoiodo-stearic acid. Penetration, as shown by printing out the sections on a photographic plate, was not as great as that demonstrated by fluorescence in the case of linoleic acid.

J. H. T. D.

THE USE OF CELLOPHANE TAPE IN THE DIAGNOSIS OF TINEA VERSICOLOR. J. A. PORTO. (1953) *J. invest. Derm.*, **21**, 229.

A Scotch tape preparation of *M. furfur* might be quite handy for teaching. Unfortunately the method is not satisfactory with erythrasma or tinea.

J. H. T. D.

MODE OF ACTION OF SELENIUM SULPHIDE. P. FLESCHE. (1953) *J. invest. Derm.*, **21**, 233.

It appears that selenium resembles arsenic in its affinity for -SH groups in liver and epidermis. It is obvious that an arsenical dandruff cure could not be popularized without some risk of its clandestine exhibition for permanent effect.

J. H. T. D.

STUDIES OF THORIUM X APPLIED TO HUMAN SKIN. III. THE RELATIVE EFFECTS OF ALPHA AND BETA-GAMMA IRRADIATION IN THE PRODUCTION OF ERYTHEMA. V. H. WITTEN, E. W. BRAUER, V. HOLSTROM and R. LOEVINGER. (1953) *J. invest. Derm.*, **21**, 249.

It certainly looks as if the clinical effect of thorium X applications must depend on the penetration of the solvent or on the diffusion of some gaseous emanation, for it did not make much difference to the very slight effect of thorium X contained in applicators whether only beta and gamma rays or alpha particles as well were allowed to escape. Qualitative differences, between the reactions produced by α , β and γ and by β and γ alone, permit the view that α particles bombarding the surface can by themselves produce erythema and pigmentation. A very thin screen of mica will, it appears, let alpha particles through and keep the thorium emanation in. Discussion brought out the odd fact that erythema-producing U.V.L. is supposed not to be able to penetrate the epidermis and that U.V.L. of 250 m μ actually fails to produce an erythema where the horny layer has been removed by means of Scotch tape.

J. H. T. D.

ATTEMPTS ON PASSIVE LOCAL SENSITIZATION BY INTRACUTANEOUS INJECTION OF CELLS FROM FRESHLY EXCISED LYMPH NODES OF ECZEMA ALLERGENS. H. HAXTHAUSEN. (1954). *J. invest. Derm.*, **21**, 237.

Another inconclusive attempt to obtain local passive transfer of allergy by means of lymphocytes. This time the lymphocytes were obtained by floating undamaged cells off the cut surfaces of lymph gland slices, the temperature being kept low and as little time lost as possible in order to secure viability.

All the patch tests were negative, but a few of the intracutaneous tests, notably those with nickel, gave a slightly more pronounced papular infiltration than when the antigen was injected into unprepared sites or saline into prepared ones.

J. H. T. D.

FURTHER OBSERVATIONS ON FACTORS WHICH INFLUENCE THE WATER CONTENT OF THE STRATUM CORNEUM. I. H. BLANK. (1953) *J. invest. Derm.*, **21**, 259.

The approximate position of the barrier to the passage of water through the horny layer seems to be that of the stratum lucidum. The rete offers no barrier at all: but pieces of plantar callosity 0.75 mm. thick allowed water to pass much more easily than epidermis from the abdomen—even after reduction of its 0.02 mm. horny layer by stripping with Scotch tape. After the lipoids have been extracted with solvents the horny layer can at first imbibe more water. But this first soaking appears to leach out at the same time a hydrophilic material without which the horny

layer not only has difficulty in taking up water again, but also requires a higher atmospheric humidity for the restoration of its flexibility. There is a difference between pyridine acetone and alcohol, which the author terms "polar" solvents, and "non-polar" solvents such as petroleum-ether turpentine and petrol. The polar solvents are much more effective in releasing this hydrophilic material for solution in water than are the non-polar solvents which are nevertheless equally effective in removing the lipid. There is evidently some chemical reaction over and above a mere degreasing action, and the author doubts if any of his findings would apply to detergents, which emulsify rather than dissolve fat.

This sort of work is of fundamental importance to the practical dermatologist who should have very little excuse for not reading this excellent paper in the original. But when the author states that the effect of the thickness of a keratin slab on the rate of diffusion through it does not follow Fick's law he must tell us what he means. Similarly if he writes of *adsorption* of water by amino imidazole and guanidyl polar groups in the protein molecule he should change to the familiar and commonly accepted word *absorption* for the mere imbibition of water by an organ such as the stratum corneum; otherwise he will frighten the more timid reader away.

The author himself, however, cannot fairly be expected to realize that his technical terms are not perfectly familiar to the reader who is possibly approaching the subject for the first time. It is the Editor's job to bring them together. J. H. T. D.

TREATMENT OF HERPES ZOSTER WITH CORTISONE. M. L. GELFAND. (1954) *J. Amer. med. Ass.*, 154, 911.

Five patients with severe acute herpes zoster were treated with oral cortisone (200 mg. in the first day, 100 mg. daily for a week and 50 mg. daily for four days). Relief of pain was dramatic in four of the five patients; the patient who experienced no relief was suffering from lymphatic leukaemia. In the four patients who responded the eruption cleared in 4 to 7 days. The author suggests that cortisone is indicated in severe cases, especially in elderly patients. A. J. R.

DERMATITIS OF THE HANDS DUE TO HOUSEHOLD CLEANERS. M. J. BRUNNER. (1954) *J. Amer. med. Ass.*, 154, 894.

Of the 145 cases of non-specific eczematous dermatitis seen by the author in a year, 108 were in housewives. He describes the familiar clinical picture and mentions circulatory, infective and emotional factors as important in aggravating and perpetuating the inflammatory reaction. The results of "simulated usage" tests are described. Detergents play a causative rôle in some cases, but the many other irritants to which the housewife is exposed are contributory. A. J. R.

TREATMENT OF KELOIDS WITH HYALURONIDASE. T. CORNBLEET. (1954) *J. Amer. med. Ass.*, 154, 1161.

The author treated 22 patients with old hard keloids by combining hyaluronidase infiltration, radiotherapy and surgical excision. One hundred and fifty units of hyaluronidase with 1 c.c. of 2% procaine solution were injected into the keloid once or twice weekly until the lesion softened. Softening, which was accompanied by a decrease in size, required from 8 to 12 injections. At this stage the keloid was excised and radiotherapy was given (90 r weekly for 8 to 12 weeks). In four other patients surgical excision was not required. The result of treatment was good in all cases and there were no recurrences. The mode of action of hyaluronidase is discussed. A. J. R.

TREATMENT OF CHRONIC DISCOID LUPUS ERYTHEMATOSUS WITH CHLOROQUINE (ARALEN). D. M. PILLSBURY and C. JACOBSON. (1954) *J. Amer. med. Ass.*, 154, 1330.

The results of treatment of 16 patients with chronic discoid erythematosus with chloroquine diphosphate 0.25-0.5 gm. daily were equal or superior to those obtained with quinaquin (mepacrine). Absence of pigmentation is an advantage and during a period of observation of 4-10 months no toxic effects were observed. A. J. R.

ESOPHAGEAL VARICES AND VASCULAR SPIDERS (NAEVI ARANEOSI) IN CIRRHOSIS OF THE LIVER. I. B. BRICK and E. D. PALMER. (1954) *J. Amer. med. Ass.*, 155, 8.

Cutaneous vascular spiders were present in 62.1% of 95 patients with cirrhosis of the liver with oesophageal varices but in only 29.1% of 55 patients with cirrhosis without varices. The presence of vascular spiders in cirrhosis is an indication for oesophagoscopy. A. J. R.